MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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TO: Solomon Iyasu, MD, MPH
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SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review: Drug Use Data
Benazepril (Lotensin®): NDA 19-851
Benazepril/HCTZ (Lotensin® HCT): NDA 20-033
Benazepril/Amlodipine (Lotrel®): NDA 20-364
Pediatric Exclusivity Approval Date: July 2, 2003

EXECUTIVE SUMMARY

This consult examines the outpatient drug use for benazepril hydrochloride, and its combination products in the pediatric population (0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on July 2, 2003.

There was an overall increase in prescriptions dispensed for the single ingredient and combination ACE inhibitor class from an estimated 122 million prescriptions in the 12-month period ending in July 2002 (8/01 – 7/02) to 133 million prescriptions in the 12-month period ending in July 2004 (8/03 – 7/04). This represented a 9.0% increase in prescriptions dispensed. While the class has experienced an increase in prescriptions dispensed, the total number of prescriptions dispensed for the single ingredient benazepril products decreased from 8.8 million prescriptions (8/01 – 7/02) to 7.2 million prescriptions (8/03 – 7/04), representing an 18.1%

decline. In contrast, the total number of prescriptions dispensed for the combination benazepril products increased from 2.0 million to 2.1 million for benazepril/HCTZ products, and 9.2 million to 12.6 million products for the benazepril/amlodipine products in that same time period. This represented approximately 7.5% and 37.7% increase, respectively. Of all the benazepril containing products, the combination benazepril/amlodipine products held the majority of the market with 57.6%, followed by the single ingredient benazpril products (32.7%) and the combination benazepril/HCTZ products (9.8%) for the 12-month period ending in July 2004.

Prescribing patterns for benazepril and its combination products dispensed in outpatient retail pharmacy settings showed that the top three prescribing specialties for these products were internal medicine (34.7%) family practice (32.8%), and osteopathic medicine (9.7%) in the most recent 12-month period ending in July 2004. The pediatric specialty represented approximately 1% of prescriptions dispensed for these products.

Between August 1, 2001 and July 31, 2004, less than 0.1% of prescription claims for benazepril and benazepril combination products were for persons aged 1-16 years among an insured population managed by Caremark. Applying the percentages from Caremark to the number of prescriptions dispensed from NPA *Plus*™, approximately 4,404 benazepril prescriptions, 654 benazepril/HCTZ prescriptions and 4,470 benazepril/amlodipine (total of 9,528 prescriptions for all products) are estimated to have been dispensed for persons aged 1-16 years in the U.S. during the time period from August 1, 2003, through July 31, 2004. Overall, in the Caremark system, the use of these products appears nearly exclusive to the adult population. Use has been stable in both populations over the past three years.

According to IMS Health, NDTI™, no pediatric use was recorded for the single ingredient benazepril or benazepril/HCTZ combination products in sampled patient-physician encounters over the past three years; however, an estimated 5,000 mentions nationally were recorded for Lotrel® (benazepril/amlodipine) in the adolescent population (ages 12-16 years) for the diagnosis of "essential hypertension unspecified" (ICD-9 code 401.9) in the most recent 12-month period ending in July 2004.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that act requires the reporting of adverse events associated with the use of the drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Benazepril hydrochloride (Lotensin®, NDA 19-851) was approved on June 25, 1991, for the treatment of hypertension. The combination products benazepril hydrochloride/ hydrochlorothiazide (Lotensin® HCT, NDA 20-033) and benazepril hydrochloride/amlodipine besylate (Lotrel®, NDA 20-364) was approved for the same indication on May 19, 1992 and March 3, 1995, respectively. The single ingredient product is available in tablet form in 5 mg, 10 mg, 20 mg, and 40 mg strengths. The hydrochlorothiazide combination product is available in tablet form in 5 mg benazepril/6.25 mg HCTZ, 10 mg benazepril/12.5 mg HCTZ, 20 mg benazepril/12.5 HCTZ and 20 mg benazepril/25 mg HCTZ strengths. The amlodipine combination product is available in capsule form in 2.5 mg benazepril/10 mg amlodipine, 5 mg benazepril/10 mg amlodipine, 5 mg benazepril/20 mg amlodipine, 10 mg benazepril/20 mg amlodipine strengths. On February 2004, generic versions of benazepril entered the market.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for benazepril hydrochloride (Lotensin®, NDA 19-851), and the combination products benazepril hydrochloride/hydrochlorothiazide (Lotensin® HCT, NDA 20-033) and benazepril hydrochloride/amlodipine besylate (Lotrel®, NDA 20-364) on July 2, 2003.

This review describes outpatient drug use patterns for benazepril and its combination products in the pediatric population as compared to the adult population in the years prior to and subsequent to the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

DATA SOURCES

Sale of these products by number of bottles and tablets sold from the manufacturer to various retail and non-retail channels of distribution were analyzed by the IMS Health, National Sales Perspectives™. Since the majority of use for these products occurs in the outpatient setting (93% of all bottles and tablets sold were to outpatient pharmacies during August 2003 through July 2004) we examined only the outpatient utilization patterns for benazepril and its combination products (Table 1). Outpatient use was measured by two IMS Health audits, the National Prescription Audit *Plus*™ (NPA *Plus*™) and the National Disease and Therapeutic Index™ (NDTI™), along with prescription claims for a 36-month period of time from Caremark (Dimension Rx™).

Table 1: Sale of Bottles (Eaches) and Tablets/Capsules (Extended Units) Sold Through Retail and Non-Retail Channels of Distribution During August 2003 – July 2004 in IMS Health, National Sales Perspectives™

	August 2003 – July 2004			
	Eaches (000)	%	Extended Units (000)	%
Benazepril (all products)	**10,235**	***100.0%***	**1,022,613**	***100.0%***
Outpatient	9,510	*92.9%*	951,259	*93.0%*
Chain Stores	4,592	*48.3%*	459,359	*48.3%*
Mail Service	1,875	*19.7%*	187,011	*19.7%*
Independent	1,869	*19.7%*	187,691	*19.7%*
Food Stores	1,174	*12.3%*	117,198	*12.3%*
Inpatient	725	*7.1%*	71,355	*7.0%*
Clinics	237	*32.7%*	23,797	*33.4%*
Long-Term Care	202	*27.9%*	20,144	*28.2%*
Non-Federal Hospitals	116	*16.0%*	10,581	*14.8%*
Federal Facilities	108	*14.9%*	10,728	*15.0%*
HMO	39	*5.3%*	3,863	*5.4%*
Miscellaneous - Prisons	11	*1.5%*	1,036	*1.5%*
Home Health Care	7	*1.0%*	696	*1.0%*
Miscellaneous-Other	4	*0.5%*	351	*0.5%*
Miscellaneous-Universities	2	*0.2%*	159	*0.2%*

National Sales Perspectives™ Retail and Non-Retail, August 2003 – July 2004, Extracted September 2004.
Original File: 0409ben2.dvr

I. OUTPATIENT DRUG USE

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database

account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis include prescriptions dispensed for benazepril and other ACE inhibitors products from August 1, 2001 to July 31, 2004, inclusive.

Caremark DIMENSION RX™

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 70 million lives, and processing over 545 million prescription claims annually. Dimension Rx™ accesses a subset of total Caremark claims, representing over 450 million prescription claims annually. People whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark manages prescription claims from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in Caremark to all persons receiving dispensed prescriptions in the U.S. is not known however.

For this analysis, annual prescription claims in the Caremark system were examined from August 1, 2001, to July 31, 2004, inclusive.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practice in the continental U.S. by collecting data on drug products mentioned during visits to office-based physicians. The data are gathered by a panel of roughly 2,000 – 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, and treatment patterns and are collected and projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of benazepril, and benazepril combination products during office-based physician visits during the time period from August 1, 2001, to July 31, 2004, inclusive.

RESULTS

I. Dispensed Prescriptions

There was an overall increase in prescriptions dispensed for the single ingredient and combination ACE inhibitor class with an estimated 122 million prescriptions in the 12-month period ending in July 2002 (8/01 – 7/02) to 133 million prescriptions in the 12-month period ending in July 2004 (8/03 – 7/04). This represented a 9.0% increase in prescriptions dispensed (Table 2). While the class experienced an increase in prescriptions dispensed, the total number of prescriptions dispensed for the single ingredient benazepril products decreased from 8.8 million prescriptions (8/01 – 7/02) to 7.2 million prescriptions (8/03 – 7/04), representing an 18.1% decline (Table 2). In contrast, the total number of prescriptions dispensed for the combination benazepril products increased from 2.0 million to 2.1 million for benazepril/HCTZ products, and from 9.2 million to 12.6 million prescriptions for the benazepril/amlodipine products in that same time period. This represented approximately 7.5% and 37.7% increase, respectively. Of all the benazepril-containing products, the combination benazepril/amlodipine products held the majority of the market with 57.6%, followed by the single ingredient benazepril products (32.7%) and the combination benazepril/HCTZ products (9.8%) for the 12-month period ending in July 2004.

Table 2: Total Number of Prescriptions (TRX) Dispensed in Retail Pharmacies (Exclude Long-Term Care Channel) for ACE Inhibitors

	Aug 01 - Jul 02		Aug 02 - Jul 03		Aug 03 - Jul 04	
	TRX (000)	*%*	**TRX (000)**	*%*	**TRX (000)**	*%*
All ACE Inhibitors	**121,720**	*100.0%*	**128,014**	*100.0%*	**133,017**	*100.0%*
ACE Inhibitor, Single Ingredient	98,200	*80.7%*	101,643	*79.4%*	103,117	*77.5%*
Benazepril	**8,782**		**8,171**		**7,174**	
ACE Inhibitor w/ Diuretic	13,807	*11.3%*	14,638	*11.4%*	16,190	*12.2%*
Benazepril/HCTZ	**1,992**		**2,081**		**2,141**	
ACE Inhibitor w/ Other	9,713	*8.0%*	11,733	*9.2%*	13,710	*10.3%*
Benazepril/Amlodipine	**9,177**		**10,955**		**12,638**	

IMS Health, National Prescription Audit *Plus*™, August 2001 – July 2004, Extracted September 2004.
Original file: 0400ben5.dvr

Prescribing patterns for benazepril and its combination products dispensed in outpatient retail pharmacy settings showed relatively little change across provider specialties from August 2001 through July 2004 (data not shown). The top three prescribing specialties for these products were internal medicine (34.7%) family practice (32.8%), and osteopathic medicine (9.7%) in the most recent 12-month period ending in July 2004 (Table 3). The pediatric specialty represented approximately 1% of prescriptions dispensed for these products.

Table 3: Total Prescriptions Dispensed by Physician Specialty (Excluding Long-Term Care and Mail Order Pharmacies)

		Aug 03 - Jul 04	
		TRX (000)	%
All Benazepril Products		**20,044**	***100.0%***
1	**Internal Medicine**	6,964	*34.7%*
2	**Family Practice**	6,583	*32.8%*
3	**Osteopathic Medicine**	1,944	*9.7%*
4	**Cardiology**	1,227	*6.1%*
5	**General Practice**	605	*3.0%*
6	**Unknown**	466	*2.3%*
7	**Nurse Practitioner**	262	*1.3%*
8	**Physicians Assistant**	222	*1.1%*
9	**Nephrology**	215	*1.1%*
10	**Pediatrics/Internal Medicine**	195	*1.0%*
11	**Endocrinology**	166	*0.8%*
12	**Emergency Medicine**	128	*0.6%*
13	**Pulmonary Diseases**	119	*0.6%*
14	**General Surgery**	114	*0.6%*
15	**Geriatrics**	87	*0.4%*
16	**Obstretrics/Gynecology**	79	*0.4%*
17	**Gastroenterology**	75	*0.4%*
18	**Oncology/Neoplastic**	53	*0.3%*
19	**Rheumatology**	50	*0.2%*
20	**Infectious Disease**	44	*0.2%*

IMS Health, National Prescription Audit *Plus*™, August 2003 – July 2004, Extracted September 2004.
Original file: 0400ben3.dvr

II. Patient Demographics

Between August 1, 2001 and July 31, 2004, less than 0.1% of prescription claims for benazepril and benazepril combination products were for persons aged 1-16 years among an insured population managed by Caremark (Table 4). The average number of claims per month for the pediatric population (age 1-16 years) remained stable at approximately 113 claims per month during August 1, 2001 through July 31, 2004. Likewise, the number of prescription claims for adults aged 17 and above also remained stable at an average of approximately 241,000 per month during that same time period.

Table 4: Total and Average Number of Claims for <u>all</u> Benazepril and Benazepril Combination Products from August 2001 – July 2004 from Caremark Pharmacy Benefit Manager Database

		Total Number of Claims	Average Claims per Month	*(%)*
August 2001 – July 2002	**Total**	**2,892,656**	**241,055**	***(100%)***
	Peds (1-16)	1,358	113	*0.05%*
	Adults (17+)	2,891,298	240,942	99.95%
August 2002 – July 2003	**Total**	**2,954,757**	**240,543**	***(100%)***
	Peds (1-16)	1,308	109	*0.04%*
	Adults (17+)	2,953,449	240,434	99.96%
August 2003 – July 2004	**Total**	**3,165,238**	**241,340**	***(100%)***
	Peds (1-16)	1,355	113	*0.04%*
	Adults (17+)	3,163,883	241,227	99.96%

Caremark Dimension Rx™, Extracted September 2004.

Since NPA Plus™ does not include demographic information on patients for the entire time period of interest, we applied the proportions for demographic subgroups from Caremark to NPA Plus™ data in an effort to approximate the number of prescriptions dispensed for benazepril and benazepril combination products nationwide to children (Table 5). Rather than using the overall proportion of use by children presented in Table 4, we stratified by product type since the proportion used by children differed slightly between products. Using this approach, approximately 4,404 benazepril prescriptions, 654 benazepril/HCTZ prescriptions and 4,470 benazepril/amlodipine (total of 9,528 prescriptions for all products) are estimated to have been dispensed for persons aged 1-16 years in the U.S. during the time period from August 1, 2003, through July 31, 2004.

Table 5: Estimated Nationwide Prescriptions Dispensed for Benazepril and Benazepril Combination Products During August 2003 – July 2004 in the Pediatric Age Group (1-16)

	August 2003 – July 2004		
	Total Number of Prescriptions* Dispensed for All Age Groups *(from Table 2)*	% Pediatric Claims** (Ages 1-16 yrs) *(from Table 4 stratified by product type)*	Estimated Number of Prescriptions Dispensed to the Pediatric Population (Age 1-16 yrs)
By product type:			
Benazepril	7,174,000	0.06%	4,404
Benazepril/HCTZ	2,141,000	0.03%	654
Benazepril/Amlodipine	12,638,000	0.04%	4,470
TOTAL			**9,528**

*IMS Health, National Prescription Audit *Plus*™, August 2001 – July 2004, Extracted September 2004. Original File: 0409ben4.dvf.
**Caremark Dimension Rx™, Extracted September 2004

Overall, in Caremark, the use of these products appears nearly exclusive to the adult population. Use has been stable in both populations over the past three years.

III. Indication for Use

According to IMS Health, NDTI™, the diagnosis, or indication, most frequently linked to benazepril use, and to benazepril combination product use, in the adult population (17 years and above) from August 2003 through July 2004, inclusive, was "essential hypertension unspecified" (ICD-9 code 401.9), accounting for 71.9%, 91.1% and 89.3% of the total benazepril, benazepril/HCTZ, and benazepril/amlodipine mentions during office-based physicians visits, respectively[1] (data not shown).

No pediatric use was recorded for the single ingredient benazepril or benazepril/HCTZ combination products in sampled patient-physician encounters over the past three years; however, an estimated 5,000 mentions nationally were recorded for Lotrel® (benazepril/amlodipine) in the adolescent population (ages 12-16 years) for the diagnosis of "essential hypertension unspecified" (ICD-9 code 401.9) in the most recent 12-month period ending in July 2004.

LIMITATIONS

NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus™ does not include historical demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include the mail order and long-term care channels. However, these channels accounted for only approximately 12% of the overall prescriptions dispensed (Calculated from Tables 1 and 2).

Caremark data cannot be projected to make national level estimates of use, but its large sample size can be helpful for replicating findings in IMS Health's NDTI™, where sample sizes are often small. Although the data from Caremark may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. Estimates of the number of prescriptions dispensed nationally to pediatric populations based on the proportion dispensed to pediatric patients in the Caremark system are dependent upon the assumption that these patterns are similar across populations with and without prescription drug coverage. The accuracy of this assumption is not known at this time. In addition, reliable information for patients less than the age of 1 year is not available from this data source.

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not prevalent in the pediatric population, as in the case of benazepril. These results should be interpreted with caution.

[1] IMS Health, National Disease and Therapeutic Index, August 2001 – July 2004, Extracted September 2004. Original File: 0409benazepril AgDx.dvf. CD ROM Source: NDTI 3 YEAR 8/01 - 7/04

CONCLUSION

There was an overall increase in prescriptions dispensed for the single ingredient and combination ACE inhibitor class with an estimated 122 million prescriptions in the 12-month period ending in July 2002 (8/01 – 7/02) to 133 million prescriptions in the 12-month period ending in July 2004 (8/03 – 7/04). This represented a 9.0% increase in prescriptions dispensed. While the class has experienced an increase in prescriptions dispensed, the total number of prescriptions dispensed for the single ingredient benazepril products decreased from 8.8 million prescriptions (8/01 – 7/02) to 7.2 million prescriptions (8/03 – 7/04), representing an 18.1% decline. In contrast, the total number of prescriptions dispensed for the combination benazepril products increased from 2.0 million to 2.1 million for benazepril/HCTZ products, and 9.2 million to 12.6 million products for the benazepril/amlodipine products in that same time period. This represented approximately 7.5% and 37.7% increase, respectively. Of all the benazepril containing products, the combination benazepril/amlodipine products held the majority of the market with 57.6%, followed by the single ingredient benazpril products (32.7%) and the combination benazepril/HCTZ products (9.8%) for the 12-month period ending in July 2004.

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